REMARKS

Claims 1-7, 9, 11-14, 21-24, 35, 39-41, 44-46 and 51-82 are pending in the subject application. Claims 1-7, 9-12, 13, 39, 44-46, 51-78 and 80-81 have been amended herein. Claims 83-85 are added. Claim 11 has been cancelled. Support for the amendment to claims 1-7, 9-12, 13, 39, 44-46, 51-78 and 80-81 and for added claims 83-85 is found throughout the Specification and claims, as filed, and no new matter is presented by the amendment.

Favorable reconsideration in light of the remarks which follow is respectfully requested.

1. 35 U.S.C. §102 Rejections

Claims 1, 7, 11, 12, 14, 21-24, 35, 41, 46 and 54 have been rejected under 35 U.S.C. §012(b) as being anticipated by German Patent No. 44 47 287 C1. The Office states that the claims are rejected for the reasons set forth in the previous Office action. Namely, the Office asserts that:

> Applicant's claims are directed toward a topical composition that is able to penetrate the pores even when the pores are smaller than the diameter of the penetrants. The composition is disclosed by applicant as being described in DE '287 (see page 2, first paragraph or applicant's specification). DE '287 refers to the composition as "transfersomes." The transfersomes in DE '287 can contain the antioxidant BHT (see English translation, page 25, second paragraph). The transfersomes can also contain glucocorticoids and mineral corticoids (see page 24 of English translation).

Applicant respectfully traverses this rejection.

Applicants claim, in amended claim 1, a formulation comprising penetrants being capable of penetrating the pores of a barrier, the average diameter of said pores being smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores, wherein the agent is selected from corticosteroids and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

As set out by Applicants, the efficacy of drug action is a multiparameter function in which the intrinsic potency, the accumulation, and the elimination kinetics of the drug all play a role. The intrinsic potency of the drug is entirely determined by the chemical composition of the drug. The accumulation and elimination kinetics of the drug are sensitive to the galenic characteristics of agent formulation and also depend on the site and rate of agent administration. (p. 2, lines 1-5) Agent carriers can be used to enable agent transport into and/or across barriers such as human skin. However, in the case of corticosteroids agents, problems relating to poor transport into and/or across the skin and galenic characteristics (formulation viscosity, chemical resistance to oxidatice degredation and/or microbiological ability) are common. (p. 4, lines 7-8) Common administration doses for various potency levels of corticosteroids can range from a few micrograms per cm^2 and up to a milligram per cm^2. If the level of corticosteroid is too low, the efficacy of the concentration-driven drug permeation into the skin is below the therapeutically acceptable level. On the other hand, if the level of corticosteroid is too high, the result may be intolerable local, or even systemic, side effects. Further, very high levels of corticosteroids is often not achievable by conventional galenic formulations. (p. 4, lines 15-20) The rate of drug transfer into the skin can be increased by raising the epidermal drug concentration, for example, by creating a local drug depot. However, highly concentrated drug solutions on the skin can result in agent precipitation on the skin and lead to undesired side-effects. The likelihood of skin irritation presents serious obstacles for the successful therapeutic application of these medications. Current skin ointments and creams typically contain large amounts of skin permeation enhancers which soften the skin. However, this is very harmful to the skin and can result in severe side effects such as skin atrophy. Thus, current galenic formulations are lacking in potency and duration of biological functions in order to avoid undesirable severe side effects. (p. 4, line 22 – p. 5, line 8)

Thus, Applicants have developed formulations based on highly adaptable carriers which are more potent and can exert its desired biological function longer than similar drugs in conventional lotions or cream form and wherein severe side effects evoked by repeat treatment are reduced or even eliminated. The present formulations have an adjustable viscosity that enables enlarged application area

and/or thickness to avoid repeated treatment. These formulations are also designed to prevent oxidative degradation and microbiological affection during storage and use.

The DE '287 reference relates to preparations for the application and the transport of active substances into and through barriers, such as the skin. The preparations are in the form of liquid droplets suspended in a liquid medium, and are surrounded by a membrane-type sheath of one or several layers of amphiphilic carrier substances with solubilities in the suspension medium differing by a factor of at least 10. (See English translation, page 10, lines 7)

In particular, according to DE '287, the preparations include at least two different amphiphile components having different solubilities (a more soluble component and a less soluble component). In one of the embodiments, it is set out that the active substance can be the more soluble component:

> Where the active substance, for example, Ibuprofin, Diclofenac or a salt thereof is the more soluble component, possibly with the addition of less than 10% by weight related to the total composition of the preparation of another soluble component and wherein the concentration of the more soluble component(s) typically amounts to between 0.01% by weight and 15% by weight. (English translation, page 25, lines 4-9)

The solubility of the components refers to their solubility in the suspension medium, which is usually water (page 10, lines 5-7).

Thus DE '287 only states that if, and only if, the active agent is the more soluble component, then it can be present in an amount between 0.01% by weight and 15% by weight. Ibuprofin and Diclofenac bear acid groups and have a relatively small apolar portion. Thus, they were specifically listed as being the more soluble components due to their polar character. In contrast, corticosteroids are relatively extended, apolar molecules, which are not at all soluble or are, at best, very poorly soluble in water. Therefore, corticosteroids are not suitable as the more soluble component in accordance with DE '287.

DE '287 does not describe or suggest that an active agent, which is an apolar substance like a corticosteroid, can be present in the presently claimed amounts. DE

'287 only describes that agents (1) that are soluble in the liquid medium (water) and (2) that are more soluble in the liquid medium (water) than the other ampophilic component can be present in an amount between 0.01% by weight and 15% by weight.

This range does not generally relate to active agents, but only to active agents acting as the more soluble component.

Applicants note that the more soluble component must be present in higher amounts such as those set out (0.01 to 15% by weight) because it must be present not only in an amount which ensures its pharmaceutical effect, but also in an amount that provides sufficient deformability to the transfersome, to enable the transfersome to penetrate through the skin. This requires a markedly higher content of active agent than is conventionally used when the active agent is not also the more soluble component.

The amounts mentioned in DE '287 thus only relate to the substances specifically mentioned, ibuprofen and diclofenac, which are capable of acting as the more soluble substance. The amounts do not generally relate also to apolar active agents like corticosteroids, which do not have the properties required for acting as the more soluble, membrane destabilising substance.

As provided in MPEP-2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Or stated another way, "The identical invention must be shown in as complete detail as is contained in the ... claims. *Richardson v Suziki Motor Co.*, 868 F.2d 1226, 9 USPQ 2d. 1913, 1920 (Fed. Cir. 1989). Although identify of terminology is not required, the elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

As set out above, the DE'287 reference does not describe or otherwise suggest a formulation containing an agent, wherein the agent is selected from corticosteroids

and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

Rather, DE'287 describes formulations containing two amphiphile components, wherein one component is the more soluble component. While DE'287 indicates that in some specific cases, the agent can be the more soluble component and that, in such a case, the more soluble component can be present in an amount between 0.01% by weight and 15% by weight, in no circumstance is the agent a corticosteroid and the corticosteroid the more soluble component. Corticosteroids are relatively extended, apolar molecules, which are not at all soluble or are, at best, very poorly soluble in the medium. Therefore, corticosteroids are not suitable as the more soluble component in accordance with DE '287. Thus, DE '287 does not describe or suggest a formulation wherein the agent is a corticosteroid and the corticosteroid is present in the amounts taught by the present invention.

Thus, it is clear from the foregoing remarks that claim 1 is not anticipated by the DE'287 reference. Claims 7, 12, 14, 21-24, 35, 41 and 46 depend from claim 1 and, likewise, are not anticipated by the DE'287 reference. Claim 11 has been canceled and, thus, rejection of this claim is moot.

6. 35 U.S.C. §103 Rejections

Claims 1-7, 9, 11-14, 21-24, 35, 39-41 and 44-46 have been rejected under 35 U.S.C. §103(a) as being unpatentable over German Pat. No. 44 47 287 C1 in view of U.S. Pat. No. 5,322,685. The Office states:

> As stated above, DE '287 teaches the claimed formulation of transfersomes. However, DE '287 does not specifically teach adding cellulose derivatives, methylparaben, and the steroid clobetasol to the composition. US '685 teaches that these ingredients are known to be used in topical formulations. Clobetasol is taught to be used topically as an anti-inflammatory (see column 2, lines 38-48). Cellulose derivatives are used to modify the viscosity of the composition and methylparaben is added as a preservative (see column 3, lines 55-59). Based on this teaching by US '685, a person of ordinary skill in the art would expect that the composition of DE '287 could be modified to include cellulose derivatives and methylparaben to improve the characteristics of the composition and to use the composition of DE '287 as a carrier for the topical steroid clobetasol. Therefore, an artisan of ordinary skill would

have been motivated to modify the composition of DE '287 to include cellulose derivatives, methylparaem, and clobetasol.

Applicant respectfully traverse this rejection.

As set out above, Applicants claim, in claim 1, a formulation comprising penetrants being capable of penetrating the pores of a barrier, the average diameter of said pores being smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores, wherein the agent is selected from corticosteroids and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

DE'287 does not describe or suggest a formulation containing corticosteroid as the active agent wherein corticosteroid is present in the formulation in the range taught by Applicant. Rather, according to DE'287, if the active agent is the more soluble component, then it can be present in an amount between 0.01% by weight and 15% by weight. As set out above, corticosteroids are relatively extended, apolar molecules, which are not at all soluble or are, at best, very poorly soluble in the medium. Therefore, corticosteroids will not be the more soluble component. Thus, there is no description in DE'287 that the corticosteroids can be present in the presently taught amounts. Further, there is no suggestion that the corticosteroids could or should be present in these amounts.

According to DE'287, the solubilities of the two amphiphile components is particularly important. As set forth, the preparations contain at least two amphiphile components that display sufficiently different solubilities, in particular, the two components differ in solubility by a factor of 10^1 to 10^7. Meeting this requirement makes it possible to ensure that the membrane-like envelope will have increased deformability, which allows the transfersomes to penetrate through permeability barriers. (See English translation, page 10, line 14 – page 11, line 2). In particular, DE'287 describes amounts of the more soluble component, which is an important value in forming the transfersomes in accordance with DE'287. The more soluble

component must be present in an amount that provides sufficient deformability to the transfersome so that the transfersome can penetrate barriers in the skin.

In conventional formulations, the active agents are present in ranges below those taught by the present invention. However, according to DE'287, the active agent can, in certain circumstances, also serve as the more soluble component. In such circumstances, the active agent must be present in amounts that the more soluble component must be present in. Accordingly, the ranges set forth are ranges required in the event that the agent serves as both the agent and as the more soluble component. As set forth above, due to their nature, in no circumstances will corticosteroids be the more soluble component. Thus, the ranges do not apply to corticosteroids, but, rather, apply only to the more soluble component and active agents that can be present as the more soluble component.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

As set forth above, all of the claim limitations are not taught or suggested by DE'287. Further, there is no suggestion or motivation to modify DE'287 as required. Rather, this suggestion comes purely from Applicants' present invention. DE'287 describes specific circumstances wherein the agent can serve as the more soluble component. In these specific circumstances, the agent can be present in amounts between 0.01% by weight and 15% by weight because these are amounts required of the more soluble component. However, there is no suggestion or motivation to provide the agent, which is not the more soluble component, in these amounts. Rather, the amount of agent conventionally added is much below the presently taught ranges.

Further, there is no reasonable expectation of success in forming a formulation wherein the agent, which is not the more soluble component, is added in these large amounts. Rather, these amounts are specific to the more soluble component. As discussed above, in no circumstances will a corticosteroid be the more soluble component.

Accordingly, Applicants respectfully submit that claim 1 is patentable over DE'287. Claims 2-7, 9, 11-14, 21-24, 35, 39-41 and 44-46 depend from claim 1 and, likewise, are patentable over DE'287.

US '685 does not remedy these deficiencies. US '685 describes a W/O cream composition comprising liquid droplets suspended in a medium for the transport of at least an active agent into and through barriers and constrictions such as the skin. The problem that US '685 focuses on solving is how to form compositions that will provide vesicles that are so deformable that they can permeate through barriers without bursting.

US '685 does not describe a formulation that includes an agent, wherein the agent is selected from corticosteroids and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

Thus, it is respectfully submitted that claim 1 is patentable over DE'287 in view of US '685.

Further, regarding the combination of DE'287 and US '685, Applicants respectfully submit that "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260,1266, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992). "The prior art must provide a motivation or reason for the worker in the art, without benefit of appellant's specification, to make the necessary changes in the reference device." *Ex parte Chicago Rawhide Mfg. Co.*, 223 USPQ351, 353 (BD. Pat. App. & Inter. 1984).

As previously set out, the US '685 preparations are W/O creams. In particular, US '685 describes a composition consisting of a diglycerol fatty acid ester and/or a sorbitan fatty acid ester and a polyvalent metal salt of a saturated or unsaturated fatty acid, which is used as emulsifier, an inorganic or organic acid salt, an oily phasee component, and water. DE'287, on the other hand, describes liposome suspensions in water. Liposome suspensions in water have completely different properties than W/O creams. Thus, US '685 describes very different types of compositions than those described by DE'287 and the present invention. Further, the US '685 reference describes methods of optimizing W/O-cream based formulations with regard to their use, stability and active agent release. Due to the different characteristics and properties of W/O cream based formulations as compared to formulations described by DE'287, different methods of optimizing these different formulations would be expected.

Thus, Applicants respectfully submit that there is no suggestion in the prior art to make the modifications suggested by the Office. Rather, the Office is improperly using hindsight reasoning view of the teachings of the present invention. Nonetheless, even if the references were combined as suggested by the Office, Applicants' invention would still not be taught or suggested. As set forth above, DE'287 does not deasribe or suggest a formulation containing corticosteroid as the active agent wherein the corticosteroid is present in the formulation in the range taught by Applicant.

Accordingly, reconsideration and withdrawal of the rejections is respectfully requested.

CONCLUSION

Reconsideration and allowance of claims 1-7, 9, 12-14, 21-24, 35, 39-41 44-46 and 51-85 is respectfully requested in view of the foregoing discussion. This case is believed to be in condition for immediate allowance. Applicant respectfully requests early consideration and allowance of the subject application.

Applicants conditionally petition for an extension of time to provide for the possibility that such a petition has been inadvertently overlooked and is required. As provided below charge Deposit Account No. **04-1105** for any required fee.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

Respectfully submitted,

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